Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A compound of the Formula Ia:

$$L$$
— $\left($ -Aa— Ww — Yy — $D\right)_p$

or a pharmaceutically acceptable salt thereof, wherein,

L- is a Ligand unit;

-A- is a Stretcher unit;

a is 1;

each -W- is independently an Amino Acid unit;

-Y- is a self-immolative Spacer unit;

w is an integer ranging from 2 to 12;

y is 1 or 2;

p ranges from 1 to about 20; and

-D is a Drug unit of the formula:

wherein, the wavy line indicates the point of attachment to the Spacer unit, and

independently at each location:

R² is selected from the group consisting of -H and -C₁-C₈ alkyl;

 R^3 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

 R^4 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, - O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) wherein; R^5 is selected from the group consisting of -H and -methyl; or R^4 and R^5 join and form a ring with the carbon atom to which they are attached and R^4 and R^5 have the formula -(CR^aR^b)_n- wherein; R^a and R^b are independently selected from the group consisting of -H, -C₁-C₈ alkyl and -C₃-C₈ carbocycle and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R⁶ is selected from the group consisting of -H and -C₁-C₈ alkyl;

 R^7 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

each R⁸ is independently selected from the group consisting of -H, -OH, -C₁-C₈ alkyl, -C₃-C₈ carbocycle and -O-(C₁-C₈ alkyl);

 R^9 is selected from the group consisting of -H and -C₁-C₈ alkyl; R^{10} is selected from the group consisting of:

 $Z \text{ is -O-, -S-,-NH- or -N}(R^{14})$ -;

Appl. No. 10/522,911 Attorney Docket No.: 018891-004310US Supplemental Amdt. dated October 2, 2009 Response to Notice of Allowance September 25, 2009

R¹¹ is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, - $C_1-C_8 \text{ alkyl, } -C_3-C_8 \text{ carbocycle, } -O-(C_1-C_8 \text{ alkyl}), \text{ -aryl, } -C_1-C_8 \text{ alkyl-aryl, } -C_1-C_8 \text{$ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); or R¹¹ is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

each R¹² is independently selected from the group consisting of -aryl and -C₃-C₈ heterocycle;

R¹³ is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, - $C_1-C_8 \text{ alkyl, } -C_3-C_8 \text{ carbocycle, } -O-(C_1-C_8 \text{ alkyl}), \text{ -aryl, } -C_1-C_8 \text{ alkyl-aryl, } -C_1-C_8 \text{ alkyl-(}C_3-C_8 \text{ alkyl-aryl, } -C_1-C_8 \text{ alkyl-a$ carbocycle), C₃-C₈ heterocycle and -C₁₋₈ alkyl-(C₃-C₈ heterocycle); and

each R¹⁴ is independently -H or -C₁-C₈ alkyl.

2-6. (Canceled)

(Currently amended) A compound of the formula Ia: 7.

or a pharmaceutically acceptable salt thereof, wherein,

L- is a Ligand unit;

-A- is a Stretcher unit;

a is 1;

each -W- is independently an Amino Acid unit;

-Y- is a self-immolative Spacer unit;

w is an integer ranging from 2 to 12;

y is 1 or 2;

p ranges from 1 to about 20; and

Appl. No. 10/522,911
Supplemental Amdt. dated October 2, 2009
Response to Notice of Allowance September 25, 2009
Attorney Docket No.: 018891-004310US

-D is a Drug unit having the structure:

or a pharmaceutically acceptable salt thereof,

wherein, the wavy line [[is]] indicates the point of attachment to the Spacer unit, and independently at each location:

R² is selected from the group consisting of -H and -methyl;

R³ is selected from the group consisting of -H, -methyl, and -isopropyl;

R⁴ is selected from the group consisting of -H and -methyl;

R⁵ is selected from the group consisting of -isopropyl, -isobutyl, -sec-butyl, -

methyl and -t-butyl or R^4 and R^5 join[[,]] and form a ring with the carbon atom to which they are attached and R^4 and R^5 have the formula -(CR^aR^b)_n- where in: R^a and R^b are independently selected from the group consisting of -H, -C₁-C₈ alkyl, and

-C₃-C₈ carbocycle, and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R⁶ is selected from the group consisting of -H and -methyl; each R⁸ is independently selected from the group consisting of -OH, -methoxy

and -ethoxy;

R¹⁰ is selected from the group consisting of:

$$R^{24}O$$
 and Z_{N}^{27} CH_{3}

 R^{24} is selected from the group consisting of H and -C(O) R^{25} -; wherein R^{25} is selected from the group consisting of -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

 $Z \ is \ -O-, \ -NH-, \ -OC(O)-, \ -NHC(O)-, \ or \ -NR^{28}C(O)-; \ {\hbox{where}} \ R^{28} \ is \ selected \ from$ the group consisting of -H and -C1-C8 alkyl;

n is 0 or 1; and

 R^{27} is selected from the group consisting of -H, -N₃, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) when n is 0; and R^{27} is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) when n is 1.

- 8. (Canceled)
- 9. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 1 where<u>in</u> -D is a Drug unit having the structure:

$$H_3C$$
 CH_3
 H_3C
 CH_3
 CH_3

10-16. (Canceled)

- 17. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 1 or claim 7 wherein the Ligand unit is an antibody.
- 18. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 17 where in the antibody is a monoclonal antibody.
- 19. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 18 wherein the monoclonal antibody specifically binds the CD30 antigen, the CD20 antigen, the Lewis X or Y antigen, the CD33 antigen, the CD38 antigen, the CEA antigen, the CD19 antigen, the CA15-3 antigen or the epidermal growth factor antigen.
- 20. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -Yy- is:

Q is selected from the group consisting of - C_1 - C_8 alkyl, -O-(C_1 - C_8 alkyl), -halogen, -nitro and -cyano; and

m is an integer ranging from 0-4, the amino terminus of -Yy- forming a bond with the Amino acid unit and the other terminus of -Yy- forming a bond with the Drug unit.

21. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 where <u>in</u> -A- is:

$$\xi = \int_{O}^{O} \int_{(CH_2)_rC(O)-\xi}^{O}$$

and r is an integer ranging from 1-10, the carbonyl terminus of -A- forming a bond with the Amino Acid unit and the succinimido terminus of -A- forming a bond with the Ligand unit.

22. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 where<u>in</u> -A- is:

$$r^{2} \xrightarrow{O} NH - (CH_{2})_{r} \xrightarrow{Z}_{Q}$$

and r is an integer ranging from 1-10, the carbonyl terminus of -A- forming a bond with the Amino Acid unit and the amidomethyl terminus of -A- forming a bond with the Ligand unit.

23. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -A- is:

$$\{ - \{ (CH_2CH_2O)_rC(O) - \{ \} \} \}$$

and r is an integer ranging from 1-10, the carbonyl terminus of -A- forming a bond with the Amino acid unit and the succinimido terminus of -A- forming a bond with the Ligand unit.

24. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -A- is:

$$N-(CH_2CH_2O)_rCH_2C(O)-\frac{2}{5}$$

and r is an integer ranging from 1-10, the carbonyl terminus of -A- forming a bond with the Amino acid unit and the succinimido terminus of -A- forming a bond with the Ligand unit.

25. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -A- is:

and r is an integer ranging from 1-10, the carbonyl terminus of -A- forming a bond with the Amino acid unit and the amidomethyl terminus of -A- forming a bond with the Ligand unit.

26. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -A- is:

$$N-(CH_2CH_2O)_rCH_2C(O)$$

the carbonyl terminus of -A- forming a bond with the Amino acid unit and the amidomethyl terminus of -A- forming a bond with the Ligand unit.

27. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 21 wherein -A- is:

$$N-(CH_2)_5CO-\frac{1}{5}$$

the carbonyl terminus of -A- forming a bond with the Amino acid unit and the succinimido terminus of -A- forming a bond with the Ligand unit.

28. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 22 where <u>in</u> -A- is:

the carbonyl terminus of -A- forming a bond with the Amino acid unit and the amidomethyl terminus of -A- forming a bond with the Ligand unit.

29. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 24 where <u>in</u> -A- is:

the carbonyl terminus of -A- forming a bond with the Amino acid unit and the succinimido terminus of -A- forming a bond with the Ligand unit.

30. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 where \underline{in} -W_w- is -Phenylalanine-Lysine-, the amino terminus of -W_w- forming a bond with the Stretcher unit and the C- terminus of -W_w-forming a bond with the Spacer unit.

31-43. (Canceled)

44. (Currently amended) A compound of the formula:

$$R^{16} \xrightarrow[R^2]{} O \xrightarrow[R^4]{} R^{5} \xrightarrow[R^6]{} R^{8} \xrightarrow[R^8]{} O \xrightarrow[R^8]{} CH_3 \xrightarrow[R^9]{} R^{11} \xrightarrow[R^12]{}$$

or a pharmaceutically acceptable salt thereof; wherein, independently at each location:

R² is selected from the group consisting of -H and -C₁-C₈ alkyl;

 R^3 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈

carbocycle, -O-(C_1 - C_8 alkoxy), -aryl, - C_1 - C_8 alkyl-aryl, - C_1 - C_8 alkyl-(C_3 - C_8 carbocycle), - C_3 - C_8 heterocycle and - C_1 - C_8 alkyl-(C_3 - C_8 heterocycle);

 R^4 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkoxy), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) wherein; R^5 is selected from the group consisting of -H and -methyl; or R^4 and R^5 join and form a ring with the carbon atom to which they are attached and R^4 and R^5 have the formula: -(CR^aR^b)_n- wherein; R^a and R^b are independently selected from the group consisting of -H, -C₁-C₈ alkyl and -C₃-C₈ carbocycle and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R⁶ is selected from the group consisting of -H and -C₁-C₈ alkyl;

 $\ensuremath{R^7}$ is selected from the group consisting of -H, -C1-C8 alkyl, -C3-C8

carbocycle, -O-(C_1 - C_8 alkoxy), -aryl, - C_1 - C_8 alkyl-aryl, - C_1 - C_8 alkyl-(C_3 - C_8 carbocycle), - C_3 - C_8 heterocycle and - C_1 - C_8 alkyl-(C_3 - C_8 heterocycle);

each R^8 is independently selected from the group consisting of -H, -OH, - C_1 - C_8 alkyl, - C_3 - C_8 carbocycle and -O-(C_1 - C_8 alkoxy);

 R^9 is selected from the group consisting of -H and -C₁-C₈ alkyl;

R¹¹ is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -

 $N(R^{14})_2$, $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, $-O-(C_1-C_8$ alkyl), -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$

Attorney Docket No.: 018891-004310US

 $(C_3-C_8 \text{ carbocycle})$, $-C_3-C_8 \text{ heterocycle}$ and $-C_1-C_8 \text{ alkyl-}(C_3-C_8 \text{ heterocycle})$; or R^{11} is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

each R¹² is independently selected from the group consisting of -aryl and -

C₃-C₈ heterocycle;

R¹³ is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -

 $N(R^{14})_2$, $-C_1$ - C_8 alkyl, $-C_3$ - C_8 carbocycle, -O- $(C_1$ - C_8 alkoxy), -aryl, $-C_1$ - C_8 alkyl-aryl, $-C_1$ - C_8 alkyl- $(C_3$ - C_8 carbocycle), $-C_3$ - C_8 heterocycle and $-C_1$ - C_8 alkyl- $(C_3$ - C_8 heterocycle);

each R¹⁴ is independently -H or -C₁-C₈ alkyl;

R¹⁶ is A'a-Ww-Yy-

wherein

each -W- is independently an Amino Acid unit;

-Y- is a self-immolative Spacer unit;

w is an integer ranging from 2 to 12;

y is 1 or 2;

-A' is a Stretcher unit; and

a is 1.

45. (Currently amended) The compound of claim 44 having the structure:

or a pharmaceutically acceptable salt thereof.

Appl. No. 10/522,911 Supplemental Amdt. dated October 2, 2009 Response to Notice of Allowance September 25, 2009

46. (Currently amended) The compound of claim 44 having the structure:

or a pharmaceutically acceptable salt thereof.

- 47. (Canceled)
- 48. (Currently amended) The compound of claim 44 having the structure:

Br
$$\rightarrow$$
 NH \rightarrow CH₃ \rightarrow C

or a pharmaceutically acceptable salt thereof.

49-51. (Canceled)

52. (Currently amended) The compound of claim 44 having the structure:

Appl. No. 10/522,911 Supplemental Amdt. dated October 2, 2009 Response to Notice of Allowance September 25, 2009

or a pharmaceutically acceptable salt thereof.

- 53. (Canceled)
- 54. (Currently amended) The compound of claim 128 having the structure:

or a pharmaceutically acceptable salt thereof.

- 55. (Canceled)
- 56. (Currently amended) The compound of claim 1 having the structure:

Appl. No. 10/522,911 Supplemental Amdt. dated October 2, 2009 Response to Notice of Allowance September 25, 2009

 H_{3} C CH_{3} H_{3} C CH_{3} H_{3} C CH_{3} CH_{3} CH_{3} CH_{3} CH_{3}

or a pharmaceutically acceptable salt thereof.

57-58. (Canceled)

59. (Currently amended) The compound of claim 1 having the structure:

or a pharmaceutically acceptable salt thereof.

60-76. (Canceled)

77. (Currently amended) The compound of claim 1 having the formula:

or a pharmaceutically acceptable salt thereof, wherein L is a monoclonal antibody.

- 78. (Canceled)
- 79. (Previously presented) The compound of claim 54 or a pharmaceutically acceptable salt thereof, wherein L is a monoclonal antibody.

80-99. (Canceled)

100. (Previously presented) The compound or pharmaceutically acceptable salt thereof of claim 79 wherein L specifically binds the CD20 antigen.

101-103. (Canceled)

104. (Previously presented) The compound or pharmaceutically acceptable salt thereof of claim 77 wherein L specifically binds the CD20 antigen.

105-110. (Canceled)

111. (Previously presented) A composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof of claim 1 or claim 7, and a pharmaceutically acceptable carrier or vehicle.

112-118. (Canceled)

- 119. (Previously presented) The compound or a pharmaceutically acceptable salt thereof of claim 1 in an isolated or a purified form.
 - 120. (Canceled)

- 121. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 where \underline{in} -W_w- is -valine-citrulline-, the amino terminus of -W_w- forming a bond with the Stretcher unit, and the C- terminus of -W_w- forming a bond with a the Spacer unit.
- 122. (Currently amended) The compound of claim 44 or a pharmaceutically acceptable salt of the compound of claim 44, wherein

-A' is selected from the group consisting of:

wherein

G is selected from the group consisting of -Cl, -Br, -I, -O-mesyl and -O-tosyl;

J is selected from the group consisting of -Cl, -Br, -I, -F, -OH, -O-N-succinimide, -O-(4-nitrophenyl), -O-pentafluorophenyl, -O-tetrafluorophenyl and -O-C(O)-OR¹⁸;

[[a is 1;]]

 R^{17} is selected from the group consisting of $-C_1-C_{10}$ alkylene-, $-C_3-C_8$ carbocyclo-, -O- $(C_1-C_8$ alkoxy)-, -arylene-, $-C_1-C_{10}$ alkylene-arylene-, -arylene- C_1-C_{10} alkylene-, $-C_1-C_{10}$ alkylene- $(C_3-C_8$ carbocyclo)-, $-(C_3-C_8$ carbocyclo)- $-C_1-C_{10}$ alkylene-, $-C_3-C_8$ heterocyclo-, $-C_1-C_{10}$ alkylene- $-(C_3-C_8)$ heterocyclo)-, $-(C_3-C_8)$ heterocyclo)- $-C_1-C_{10}$ alkylene-, $-(C_3-C_8)$ heterocyclo)-, and $-(C_3-C_8)$ heterocyclo)-, $-(C_3-C_8)$ heterocyclo)- $-(C_3-C_8)$ heterocyclo

r is an integer ranging from 1-10; and

 R^{18} is $-C_1-C_8$ alkyl or -aryl.

- 123. (Canceled)
- 124. (Previously presented) A composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof of claim 79 and a pharmaceutically acceptable carrier or vehicle.
- 125. (Previously presented) A composition comprising an effective amount of a compound or a pharmaceutically acceptable salt thereof of claim 121 and a pharmaceutically acceptable carrier or vehicle.
- 126. (Previously presented) The compound or a pharmaceutically acceptable salt thereof of claim 79 in an isolated or a purified form.
- 127. (Previously presented) The compound or a pharmaceutically acceptable salt thereof of claim 121 in an isolated or a purified form.
- 128. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein

-Aa-Ww-Yy- has the formula:

the succinimido terminus forming a bond with the Ligand unit and the other terminus forming a bond with the Drug unit.

129. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claim 7 wherein

-Aa-Ww-Yy- has the formula:

the succinimido terminus forming a bond with the Ligand unit and the other terminus forming a bond with the Drug unit.

- 130. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claims 128 or 129 wherein the ligand unit is a monoclonal antibody.
- 131. (Currently amended) The compound or pharmaceutically acceptable salt thereof of claim 1 where \underline{in} R¹⁰ is

132. (Currently amended) The compound or pharmaceutically acceptable salt thereof of claim 7 where \underline{in} R^{10} is:

- 133. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claim 19 wherein the monoclonal antibody specifically binds the CD30 antigen.
- 134. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claim 19 wherein the monoclonal antibody specifically binds the CD19 antigen.
- 135. (Previously presented) The compound or a pharmaceutically acceptable salt of the compound of claim 19 wherein the monoclonal antibody specifically binds the CD33 antigen.
- 136. (Currently amended) The compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein -A_a- is:

wherein R^{17} is selected from the group consisting of $-C_1-C_{10}$ alkylene, C_3-C_8 carbocyclo-, $-O-(C_1-C_8$ alkyl)-, -arylene-, $-C_1-C_{10}$ alkylene-arylene-, -arylene- C_1-C_{10} alkylene-, $-C_3-C_8$ carbocyclo)-, $-(C_3-C_8$ carbocyclo)- $-C_1-C_{10}$ alkylene-, $-C_3-C_8$ heterocyclo-, $-C_1-C_{10}$ alkylene- $-(C_3-C_8)$ heterocyclo-, $-(C_3-C_8)$ heterocyclo)- $-(C_3-C_8)$ heterocyclo)-

- 137. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 1 wherein p ranges from 1 to about 5.
- 138. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 79 wherein p ranges from 1 to about 5.
- 139. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 54 where<u>in</u> L is a monoclonal antibody that specifically binds the CD30 antigen, the CD20 antigen, the Lewis X or Y antigen, the CD33 antigen, the CD19 antigen, the CD38 antigen, the CEA antigen, the CA15-3 antigen or the epidermal growth factor antigen.
- 140. (Currently amended) [[A]]<u>The</u> compound or a pharmaceutically acceptable salt of the compound of claim 139 wherein the monoclonal antibody specifically binds the CD30 antigen.
- 141. (Currently amended) A composition comprising drug-linker-ligand conjugates having Formula Ia:

$$L - \left(A_{\overline{a}} W_{\overline{w}} Y_{\overline{y}} - D \right)_{p}$$
Ia

Attorney Docket No.: 018891-004310US

or a pharmaceutically acceptable salt thereof; wherein,

L- is a Ligand unit;

-A- is a Stretcher unit;

a is 1;

each -W- is independently an Amino Acid unit;

-Y- is a self-immolative Spacer unit;

w is an integer ranging from 2 to 12;

y is 1 or 2;

p ranges from 1 to about 5 and is the average number of $-A_a$ - W_w - Y_y -D units per ligand in the composition; and

-D is a Drug unit of the formula:

wherein, the wavy line indicates the point of attachment to the Spacer unit, and independently at each location:

R² is selected from the group consisting of -H and -C₁-C₈ alkyl;

 R^3 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

 R^4 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) wherein; R^5 is selected from the group consisting of -H and -methyl; or R^4 and R^5 join and form a ring with the carbon atom to which they are attached and

Attorney Docket No.: 018891-004310US

 R^4 and R^5 have the formula - $(CR^aR^b)_n$ - wherein; R^a and R^b are independently selected from the group consisting of -H, -C₁-C₈ alkyl and -C₃-C₈ carbocycle and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R⁶ is selected from the group consisting of -H and -C₁-C₈ alkyl;

 R^7 is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl,

-C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

each R^8 is independently selected from the group consisting of -H, -OH, -C₁-C₈ alkyl, -C₃-C₈ carbocycle and -O-(C₁-C₈ alkyl);

 R^9 is selected from the group consisting of -H and -C₁-C₈ alkyl; R^{10} is selected from the group consisting of:

Z is -O-, -S-,-NH- or -N(R^{14})-;

 R^{11} is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); or R^{11} is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

each R^{12} is independently selected from the group consisting of -aryl and -C₃-C₈ heterocycle;

R¹³ is selected from the group consisting of -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), C₃-C₈ heterocycle and -C₁₋₈ alkyl-(C₃-C₈ heterocycle); and each R¹⁴ is independently -H or -C₁-C₈ alkyl.

Attorney Docket No.: 018891-004310US

142. (Currently amended) A composition comprising drug-linker-ligand conjugates having Formula Ia:

$$L - \left(A_{\overline{a}} - W_{\overline{w}} - Y_{\overline{y}} - D \right)_{p}$$
Ia

or a pharmaceutically acceptable salt thereof wherein,

L- is a Ligand unit;

-A- is a Stretcher unit;

a is 1;

each -W- is independently an Amino Acid unit;

-Y- is a self-immolative Spacer unit;

w is an integer ranging from 2 to 12;

y is 1 or 2;

p ranges from 1 to about 5 and is the average number of - A_a - W_w - Y_y -D units per ligand in the composition; and

-D is a Drug unit having the structure:

or a pharmaceutically acceptable salt thereof,

wherein, the wavy line [[is]]indicates the point of attachment to the Spacer unit, and independently at each location:

R² is selected from the group consisting of -H and -methyl;

R³ is selected from the group consisting of -H, -methyl, and -isopropyl;

R⁴ is selected from the group consisting of -H and -methyl;

 R^5 is selected from the group consisting of -isopropyl, -isobutyl, -sec-butyl, - methyl and -t-butyl or R^4 and R^5 join[[,]] and form a ring with the carbon atom to which they are attached and R^4 and R^5 have the formula - $(CR^aR^b)_n$ - where in; R^a and R^b are independently selected from the group consisting of -H, -C₁-C₈ alkyl, and

-C₃-C₈ carbocycle, and n is selected from the group consisting of 2, 3, 4, 5 and 6;

R⁶ is selected from the group consisting of -H and -methyl; each R⁸ is independently selected from the group consisting of -OH, -methoxy

R¹⁰ is selected from the group consisting of:

$$R^{24}O$$
 and $(Z)_nR^{27}$

 R^{24} is selected from the group consisting of H and -C(O) R^{25} -; wherein; R^{25} is selected from the group consisting of -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);

Z is -O-, -NH-, -OC(O)-, -NHC(O)-, or -NR 28 C(O)-; where; R^{28} is selected from the group consisting of -H and -C₁-C₈ alkyl;

n is 0 or 1; and

and -ethoxy;

PATENT Attorney Docket No.: 018891-004310US

 R^{27} is selected from the group consisting of -H, -N₃, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle) when n is 0; and

 R^{27} is selected from the group consisting of -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -aryl, -C₁-C₈ alkyl-aryl,

 $-C_1-C_8$ alkyl- $(C_3-C_8$ carbocycle), $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl- $(C_3-C_8$ heterocycle) when n is 1.

143. (Currently amended) The composition of claim 141 wherein <u>in the drug-linker-ligand conjugates or pharmaceutically acceptable salt thereof</u>, R¹⁰ is

144. (Currently amended) The composition of claim 142 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, R¹⁰ is

145. (Currently amended) The composition of claim 141 where <u>in in the drug-linker-ligand conjugates or pharmaceutically acceptable salt thereof,</u> -D is a Drug unit having the structure:

÷

or a pharmaceutically acceptable salt thereof.

146. (Currently amended) The composition of claim 141 wherein <u>in the drug-linker-ligand conjugates or pharmaceutically acceptable salt thereof</u>, -Aa-Ww-Yy- has the formula:

$$\begin{array}{c|c}
H_2N & O \\
NH & NH
\end{array}$$

the succinimido terminus forming a bond with the Ligand unit and the other terminus forming a bond with the Drug unit.

147. (Currently amended) The composition of claim 142 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, -Aa-Ww-Yy- has the formula:

the succinimido terminus forming a bond with the Ligand unit and the other terminus forming a bond with the Drug unit.

- 148. (Currently amended) The composition of claim 141 where<u>in in the drug-linker-ligand conjugates or pharmaceutically acceptable salt thereof</u>, the ligand unit is a monoclonal antibody.
- linker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD30 antigen, the CD20 antigen, the CD19 antigen, the Lewis X or Y antigen, the CD33 antigen, the CD38 antigen, the CEA antigen, the CA15-3 antigen or the epidermal growth factor antigen.
- 150. (Currently amended) The composition of 149 wherein in the drug-linker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD19 antigen.
- 151. (Currently amended) The composition of claim 149 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD30 antigen.
- 152. (Currently amended) The composition of claim 149 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD33 antigen.

153. (Currently amended) The composition of claim 147 wherein the druglinker-ligand conjugates have the formula:

or a pharmaceutically acceptable salt thereof.

- 154. (Currently amended) The composition of claim 153 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, L is a monoclonal antibody.
- 155. (Currently amended) The composition of claim 154 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD20 antigen, the CD30 antigen, the CD33 antigen, the CD19 antigen, the CD38 antigen, the CA15-3 antigen, the CEA antigen, or the epidermal growth factor antigen.
- 156. (Currently amended) The composition of claim 155 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the the CD30 antigen.
- 157. (Currently amended) The composition of claim 155 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD19 antigen.
- 158. (Currently amended) The composition of claim 155 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD20 antigen.

- 159. (Currently amended) The composition of claim 155 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD33 antigen.
- 160. (Currently amended) The composition of claim 142 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, L is a monoclonal antibody.
- 161. (Currently amended) The composition of claim 160 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD20 antigen, the CD30 antigen, the CD33 antigen, the CD19 antigen, the CD38 antigen, the CA15-3 antigen, the CEA antigen, or the epidermal growth factor antigen.
- 162. (Currently amended) The composition of claim 161 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the monoclonal antibody specifically binds the CD30 antigen.
- 163. (Currently amended) The composition of claim 154 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, the antibody is attached to the drug moiety through a cysteine residue of the antibody.
- 164. (Currently amended) The compound of claim 122 or a pharmaceutically acceptable salt of the compound of claim 122, wherein

A_a- is:

wherein R^{17} is selected from the group consisting of $-C_1-C_{10}$ alkylene, C_3-C_8 carbocyclo-, $-O-(C_1-C_8$ alkyl)-, -arylene-, $-C_1-C_{10}$ alkylene-arylene-, -arylene- C_1-C_{10} alkylene-, $-C_3-C_8$ carbocyclo)-, $-(C_3-C_8$ carbocyclo)- $-C_1-C_{10}$ alkylene-, $-C_3-C_8$ heterocyclo-

- , -C₁-C₁₀ alkylene-(C₃-C₈ heterocyclo)-, (C₃-C₈ heterocyclo)-C₁-C₁₀alkylene-, -(CH₂CH₂O)_r-, and -(CH₂CH₂O)_r-CH₂-; and r is an integer ranging from 1-10.
- 165. (Currently amended) The compound of claim 1 or a pharmaceutically acceptable salt of the compound of claim 1 wherein R^2 is $-C_1-C_8$ alkyl.
- 166. (Currently amended) The composition of claim 141 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, R^2 is $-C_1-C_8$ alkyl.
- 167. (Currently amended) The compound of claim 7 or a pharmaceutically acceptable salt of the compound of claim 7 wherein R^2 is -methyl.
- 168. (Currently amended) The composition of claim 142 wherein in the druglinker-ligand conjugates or pharmaceutically acceptable salt thereof, R² is -methyl.